Original Article

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Assessment of Growth Parameters in Transfusion Dependent Thalassemicsat A Tertiary Care Hospital

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ABSTRACT

Background: Thalassemia is a group of genetic blood disorders all of which involve under production of haemoglobin , and partial or complete failure of synthesis a specific type of globin chain . Thalassemia major is most common monogenic disorder in the world. Around 1,00,000 children are born each year with the severe homozygous state of the disease in India. The objectives of this study was to assess clinical data and the growth parameters of thalassemia major patients attending tertiary care hospital.Beta Thalassemia Major (BTM) is transfusion dependent state where physical growth is affected in majority of patients. This study will emphasize to assess iron overload and growth parameters of transfusion dependent BTM patients. This was undertaken as very few studies have been done in this region of the our country.

Methods: The study was done at a tertiary care teaching hospital from January 2014 to December 2014. Universal sampling method was used and 31 β thalassemia major patients who received blood transfusions at 2 to 4 weeks interval in the hospital were included in this study. Clinical details and blood transfusion record was collected on proforma for all patients and data interpreted. This study was done on 31 known diagnosed BTM patients with age 10 years and above. Height, weight, BMI along with hemoglobin and serum ferritin were estimated. IAP growth charts were plotted for various parameters. Appropriate statistical tests were used for analysis.

Result: Of 31 patients, 25 were males and 6 were females . Age range was 10 -18 years with mean age of 12.45 years. There were 20(64.5%) patients not taking chelation. Mean and SD of pretransfusion hemoglobin of all patients was 6.85±1.13 gm%. Mean and SD of ferritin of all patients, nonchelated and chelated patients was 3786 ±2382 ng/ml, 4505±2633 ng/ml and 2479 ± 963.6 ng/ml respectively. Weight for Age (W/A)charts of males and females showed 28% and 16.6 % respectively below 3rd percentile. Height for age (H/A) charts of males showed 40 % below 3rd percentile and none of the females below 3rd percentile. BMI of males and females showed 20% and 50% respectively below 3rd percentile. Most of the patients were of short stature and underweight indicating growth failure.

Conclusion: The present study describes the growth parameters of β thalassemia major patients attending the tertiary care hospital and emphasizes on maintenance of growth charts of these patients for better management. Growth failure in BTM is mainly due to iron overload and chronic anemia. This study emphasizes the need of screening for growth failure, regularly estimating iron overload and its control by chelation therapy.

Keywords: *Thalassemia Major, Growth Failure, Percentile, Chelation*

Introduction

Thalassemia is a group of genetic blood disorder all of which involve under production of haemoglobin, and partial or complete failure of synthesis a specific type of globin chain. The defect may affect the α, γ and δ chain or may affect some combination of the β, γ and δ chain in the same patient, but never α and β chain together, unmatched globins precipitate and damage red blood cell membranes causing their destruction while still in the marrow[1,2]. β thalassemia is caused by the reduced (β^+) or absent (β^0) synthesis of the β globin chains of the hemoglobin tetramer, which is made up of two α globin and two β globin chains ($\alpha_2\beta_2$). Three clinical and hematological conditions of increasing severity are recognized, i.e., β thalassemia carrier state, thalassemia intermedia, and thalassemia major.[3]About 7% of the world's population is a carrier of a hemoglobin disorder. Each year about 3,00,000-5,00,000 children are born worldwide with the severe heterozygous state of the disease. [4] About 1,00,000 are born with thalassemia in India.[5] These patients with BTM require regular blood transfusions to survive. Regular transfusion with packed red cells is recommended to maintain a pretransfusion hemoglobin threshold not exceeding 9.5 g/dl. This seems to be associated with adequate marrow inhibition and a relatively low iron burden.[6]

Regular red blood cell (RBC) transfusions eliminate the complications of anemia and compensatory bone marrow (BM) expansion, permit normal development throughout childhood, and extend survival. Transfusions result in iron overload, which is fatal without treatment in the second

decade of life. Iron-chelating therapy for iron overload is one important part of major thalassemia treatment in last 20 years.[7] Endocrine dysfunction is recognized in patients with transfusion dependent thalassemia, which causes by iron overload.[8]The most common endocrine abnormalities in patients with thalassemia include hypogonadotropic hypogonadism, growth hormone deficiency, and diabetes mellitus.[8,9] Growth impairment is commonly seen in children with thalassemia with regular blood transfusions and desferrioxamine treatments.[10]The child with BTM has a particular growth pattern, which is relatively normal until age 9–10 years; after this age a slowing down of growth velocity and a reduced or absent pubertal growth spurt are observed. Growth failure has been attributed to growth hormone, insulin-like growth factor 1(IGF-1), insulin-like growth factor binding protein 3 deficiency, hypothyroidism, delayed sexual maturation and bone disorders caused by desferrioxamine toxicity.[11] There is lack of data in this region of India which provides description of growth parameters of β thalassemia major patients. Accordingly, the present study was undertaken to assess the various growth parameters in transfusion dependent β thalassemia major patients.

Materials and Methods

The present cross-sectional study was done at a tertiary care hospital from January 2014 to December 2014. 31 β thalassemia major patients who received blood transfusions were selected using universal sampling method during the study period. Ethical clearance for the study was obtained from the Institute ethics committee. The objectives of this study were assessment of growth parameters using growth charts, assessment of iron overload by estimating serum ferritin and find association between serum ferritin with growth parameters. All known diagnosed cases of **β thalassemia major** who are 10 years of age and above, and have received blood transfusions at two to four weeks intervals with or without iron chelation therapy in the tertiary care hospital were included in the study. Thalassemia International Federation guidelines recommends age group of 10 years and above for screening growth retardation and treatment of growth in sufficiency.

Exclusion criteria in this study were patients who are known cases of other types of thalassemias and hemoglobinopathies and patients diagnosed with growth related disorders like endocrine diseases.. The clinical examination was done for all patients. Blood transfusion data was collected in detail. Proforma consisted of data regarding total number of blood transfusions during lifetime, number of transfusions per month and Chelation therapy. Hemoglobin estimation was done for all patients. Weight by Age (W/A), Height by Age (H/A) and Body Mass Index (BMI) for age were plotted for all patients. Growth assessment using Revised Indian Association of Pediatrics (IAP) growth charts 2014 was done. Growth charts were assessed by plotting parameters as per the IAP charts and compared with the standards for age and sex and inference derived. The data obtained was coded and entered into Microsoft Excel Spreadsheet. The data was analyzed using SPSS version 20. Categorical data was expressed in terms of rates, ratios and percentage. Continuous data was expressed as Mean ± standard deviation, median and range. Growth charts were plotted as per the reference plots.

Result

A total of 31 patients registered under Blood Bank with β thalassemia major were included in the study. The mean age was 12.45±2.38 years and median age was 12 years with younger patients being 10 years and oldest being 18 years as shown in Table1 . Majority (83%) of the patients were males and the male to female ratio was 5:1 shown in Table 2. The commonest age group was 10 to 12 years, comprised of 58.06 % of the patients followed by 13-15 years age group (29.03 %). Majority of the patients received one transfusion per month (91.43%) as shown in Table 1. Majority (64.52 %) of patients were not on chelation therapy. The mean hemoglobin and serum ferritin among all the patients , males and females is depicted in Table 3. Mean hemoglobin of all the patients was 6.85 ± 1.08 gm%. The mean hemoglobin among males was less as compared to females. Mean serum ferritin of all patients was markedly raised 3786 ±2382 ng/mL with mean ferritin higher among females (4411±1299 ng/mL) as compared to males (3636±2572 ng/mL). Similarly ferritin was markedly increased in Non-chelated group (4505±2633 ng/mL) as compared to chelated group of patients (2479±963 ng/mL) as shown in Table 3.IAP charts for males were prepared. W/A charts in males showed 28% were below 3rd percentile and none were above 97th percentile. Majority (36%) were in the 10^{th} – 25^{th} percentile (Table 4). H/A charts of males showed 40 % were below 3rd percentile and none were above 97^{th} percentile as shown in Table 5. BMI charts revealed majority (36%) in 25-50^{th} percentile and 20% below 3rd percentile as shown in Table 6.IAP charts for females were prepared. W/A charts showed 16.6 % were below 3rd percentile and none were above 97^{th} percentile. Majority (66.8 %) were in the 3^{rd} –10^{th} percentile. H/ A among girls showed none were below 3rd percentile and above 97th percentile. Majority (50%) were in 3rd – 10th percentile BMI of females revealed majority (50%) below 3rd percentile.

Table 1: Age distribution and transfusion profile of patients.

Variable			Median	Range	
	Mean	SD		Min	Max
Age (Years)	12.45	2.38	12	10	18
Age at diagnosis (Months)	8.94	6.15	8	3	36
Frequency of transfusion (/Month)	1.09	0.28	1	1	2
Total number of blood transfusions	**151.40**	**45.65**	**139**	**92**	**288**

Table 2: Gender and age wise distribution of patients.

Variables	Sub-groups	Total	
		No.	%
Sex	Male	26	80.00
	Female	05	20.00
	Total	31	100.00
Age group	10 to 12	18	58.06
(Years)	13 to 15	09	29.03
	16 to 18	04	12.91
	Total	**31**	**100.00**

Table 3: Hemoglobin and Serum ferritin of the patients.

Variables	Mean	
	Mean	SD
Hemoglobin (gm%)	6.85	1.08
Hemglobin – Males(gm%)	6.8	1.20
Hemoglobin – Females (gm%)	7.08	0.83
S.ferritin - All patients (ng/mL)	3786	2382
S. ferritin - Males (ng/mL)	3636	2572
S. ferritin - Females (ng/mL)	4411	1299
S.ferritin (Non Chelated) ng/mL	4505	2633
S. ferritin (Chelated) ng/mL	2479	963.6

Table 4: Weight for Age (W/A) charts of males and females.

GROUPS	IAP PERCENTILES	MALE	PERCENTAGE	FEMALE	PERCENTAGE
Group I	<3	7	28	1	16.6
Group II	3-10	6	24	4	66.8
Group III	10-25	9	36	1	16.6
Group IV	25-50	2	8	0	0
Group V	50-75	1	4	0	0
Group VI	75 – 90	0	0	0	0
Group VII	90-97	0	0	0	0
Group VIII	> 97	0	0	0	0

Table 5: Height for age (H/A) charts of males and females.

GROUPS	IAP PERCENTILES	MALE	PERCENTAGE	FEMALE	PERCENTAGE
Group I	<3	10	40	0	0
Group II	3-10	8	32	3	50
Group III	10-25	4	16	0	0
Group IV	25-50	1	4	1	16.6
Group V	50-75	1	4	2	33.7
Group VI	75 – 90	1	4	0	0
Group VII	90-97	0	0	0	0
Group VIII	> 97	0	0	0	0

Table 6: BMI of males and females.

GROUPS	IAP PERCENTILES	MALE	PERCENTAGE	FEMALE	PERCENTAGE
Group I	<3	5	20	3	50
Group II	3-5	1	4	0	0
Group III	5-10	1	4	1	16.6
Group IV	10-25	6	24	1	16.6
Group V	25-50	9	36	1	16.6
Group VI	>50	3	12	0	0

Discussion

The genetic heterogeneity of Thalassemia results in a wide spectrum of clinical phenotypes that may vary from mild chronic hemolysis to a severe transfusion-dependent hemolytic anemia.[12] β thalassemia major is a homozygous state which causes hemolytic anemia which requires regular blood transfusions. Availability of safe blood transfusions with chelation therapy has improved and extended the survival rates of these patients. The life expectancy in thalssemics has now escalated to fourth and fifth decades. If a regular transfusion program that maintains a minimum hemoglobin concentration of 9.5 to 10.5 g/dL is begun, development and growth tends to be normal up to 10 to 12 years.[13] Transfused patients may develop complications related to iron overload. Complications of iron overload in children include growth retardation and failure or delay of sexual maturation. Patients not receiving regular transfusions usually die in second or third decade of their life. However, patients who have been regularly transfused and receiving appropriate chelation therapy survive beyond 40 years of age.[14]In this study the mean age observed in the present study was close to that of Chern et al. [15] (14.8 ± 6.9 years) and a study by Khalifa et al [16] (15.9 ± 3.1 years). In a study by Najafipour F et al. [17] in Iran reported mean age was 15.62 ± 4.44 with youngest patient being 10 years and oldest being 27 years. Majority of the patients (83%) in this study were males with male to female ratio of 5:1. A study done in Italy, involving 250 patients aged 10-25 years, 37% were found to be 2 SD below the mean for normal height and weight, while in patients over 14 years of age, the percentage was 62% for males and 35% for females.[18] In a study at AIIMS, New Delhi various growth parameters of 233 thalassemic children were compared with 74 non-thalassemic siblings, ICMR and NCHS norms. Weight and height were retarded in thalassemic children.[19] Majority of the patients in our study were anemic and non-chelated with iron overload, short stature and underweight indicating growth retardation and growth failure. A study done by Hamidah and coworker on 26 prepubertal patients with beta-thalassemia or HbE-beta thalassemia who were transfusion dependent. The mean serum Ferritin level of the thalassemic patients with a height < 3rd percentile was higher compared to patients with a height > 3rd percentile (4,567 ng/mL vs. 2,271 ng/mL , P-value = 0.01). [20]Growth retardation is commonly reported in children and adolescents with BTM. Pathogenesis of growth failure is multifactorial: chronic anaemia, transfusional iron overload, hypersplenism, and chelation toxicity. Other contributing factors include hypothyroidism, hypogonadism, growth hormone deficiency/insufficiency, zinc deficiency, chronic liver disease, under nutrition and psycho-social stress. Growth disturbance are a major clinical feature of untreated patient with thalassemia. The fundamental problem is free iron within expanded labile pool. It is shown that heart and pituitary are especially sensitive to free iron toxicity. Characteristically three

phases of growth according to age of presentation are recognized which have different etiologies. The first phase of childhood growth disturbance is mainly due to hypoxia, anemia, and nutritional factors. The second phase is due to anemia and iron load affecting GH-IGF axis. The hormonal cause of growth retardation in TM children is complex. It has been apparent that GH-IGF-1 axis plays a role in their abnormal growth besides hypogonadism and hypothyroidism. However, most patients present after the age of 10–11 years (3rd phase) with peripubertal growth and pubertal disturbance with absence of growth spurt, arrested and absent puberty with growth retardation.[21]This is usually due to iron load affecting H-P-G axis. GH-IGF axis may also be affected. Characteristically, patients frequently present with severe delay/absence of puberty with reduction of final height.Chronic hypoxia is no longer a contributing factor in properly treated children. Linear growth in childhood is disrupted only in a small percentage of children due to anemia, ineffective erythropoiesis and iron overload. During the first decade of life the maintenance of hemoglobin levels above 9 g/dL together with adequate iron chelation therapy makes the children with TM indistinguishable from their non-thalassemic peers.[11] The increasing mean survival age is indicative of the fact that modern therapies are generally safe and effective but it is becoming increasingly clear that as thalassemic patients approach the age of puberty, many develop growth retardation and pubertal failure.

Conclusion

Overall, the present study describes the growth parameters of thalassemia major patients. These patients need comprehensive care. Growth retardation in children with BTM is evident despite regular transfusions and chelation therapy, especially in children with older age. The etiology of growth retardation in BTM patients is likely to be multifactorial These children must be assessed for growth retardation at appropriate age using Indian Association of Pediatrics (IAP) charts representative of Indian population and treated accordingly as per guidelines of Thalassemia International Federation.

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